REMARKS

This Amendment is submitted in response to the November 7, 2008 Office Action issued by the United States Patent and Trademark Office. This Office Action followed an October 29, 2008 telephonic interview among Examiners Jon Weber and Bin Shen and applicant's undersigned representative Robert Alderson. In the telephonic interview agreement was reached that the October 16, 2008 Final Office Action previously issued by Examiner Shen would be withdrawn along with the rejection of the claims under 35 U.S.C. § 103(a). In the November 7, 2008 Office Action the Examiner withdrew the 35 U.S.C. § 103(a) rejection stating that McMahon taught away from the presently claimed invention. Applicant's representative wishes to take this opportunity to express his appreciation for the courtesy extended by both Examiners during the October 29, 2008 telephone conference and for timely issuing a new non-final Office Action.

Support for new claims 26-29 may be found throughout the specification. Support for the new claims will be discussed in more detail below. No new matter is introduced by the addition of new claims 26-29. Upon entry of this Amendment new claims 26-29 will be pending in the instant application.

Rejection of Claims Under 35 U.S.C. § 112, first paragraph

In November 7, 2008 Office Action, the Examiner maintained the rejection of the claims under 35 U.S.C. § 112, first paragraph as first articulated in the October 16, 2008 Final Office Action. The Examiner alleged that the specification does not provide support for the washout period limitation included in the then pending claims.

In response, applicant respectfully traverses the rejection of the claims under 35 U.S.C. § 112, first paragraph. Without conceding the appropriateness of the Examiner's

rejection of the claims under 35 U.S.C. § 112, first paragraph, applicant has hereinabove amended the claims to state more specifically describe the nature of the washout period and how it is avoided. Applicant maintains that the specification supports the washout limitation as previously and presently claimed.

Claims 26 and 27 are the only currently pending independent claims and recite, respectively:

> A method of treating a hypertensive subject having a normal to above normal plasma renin activity level comprising:
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> A. administering to the subject or instructing the subject to take a low dose of an R drug;
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> B. after step A, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take an increased dose of the R drug;
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> C. after step B, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take, instead of the R drug, a low dose of a V drug; and
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> D. after step C, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take an increased dose of the V drug,
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> wherein said subject had been taking at least one anti-hypertensive drug prior to measuring the normal to above normal plasma renin activity level and wherein said method does not require the subject to discontinue use of the at least one anti-hypertensive drug prior to measuring the normal to above normal plasma renin activity level.
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> A method of treating a hypertensive subject having a normal to below normal plasma renin activity level comprising:

A. administering to the subject or instructing the subject to take a low dose of an V drug;

B. after step A, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take an increased dose of the V drug;

C. after step B, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take, instead of the V drug, a low dose of a R drug; and

D. after step C, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take an increased dose of the R drug,

wherein said subject had been taking at least one anti-hypertensive drug prior to measuring the normal to below normal plasma renin activity level and wherein said method does not require the subject to discontinue use of the at least one anti-hypertensive drug prior to measuring the normal to below normal plasma renin activity level.

Accordingly, new claims 26 and 27 make clear that the presently claimed invention relates, in part, to the ability to use the claimed methods in a subject already receiving at least one anti-hypertensive drug without the need for discontinuing use of such drug prior to measurement of the subject's plasma renin activity level. Applicant notes that discontinuing a drug prior to measurement of a subject's plasma renin activity level, for example, is conventionally known as a washout period.

There is ample support for the language of the new claims throughout the specification. Indeed one of the major advantages provided by the presently claimed invention, and discussed in detail in applicant's specification, is the ability to immediately begin directing a

logical course of treatment for any given hypertensive subject based on an initial PRA measurement.

Applicant provides below representative selections from the specification which provide abundant support for the new claims. Applicant points out that the citations provided below refer to a subject already taking at least one anti-hypertensive drug prior to measurement of the subject's plasma renin activity level. The subject's plasma renin level can (and should) be measured immediately without waiting through a washout period of two weeks or more. Based on such immediate measurements, a rational course of treatment can be devised. For the Examiner's convenience all cites to paragraph numbers refer to applicant's published application 2005/0090752.

First, under the heading "Protocol II: Using Plasma Renin Activity (PRA) to Guide Treatment of Unsuccessfully Treated Patients" (at paragraph 111), the specification states at paragraphs 112 and 113:

> As indicated by FIG. 5 and Table 7 below, another exemplary embodiment of the Laragh Method is quite useful for determining which drug or drugs to select for the previously unsuccessfully treated hypertensive patient. The Laragh Method can be used for (a) patients on one or more V drugs, (b) patients on one or more R drugs, or (c) patients receiving one or more R and V drugs. As was the case for Protocol I, an exemplary embodiment of Protocol II may comprise a series of steps or visits.
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> Visit 1 (as in Protocol I) may comprise measuring BP and drawing blood to test PRA levels. The appropriate action to take during Visit 2 is dependent on the PRA level. If the PRAlevel is below 0.65 ng/ml/hr and the patient is on a V drug alone, the patient may be treated consistent with the V side of Protocol I (FIG. 4), Visit 3 or 4. If the PRA level is below 0.65 ng/ml/hr and the patient is on an R drug alone, the R drug may be discontinued and treatment with a V drug initiated. This patient in Visit 3 will have his or her BP checked. If BP is controlled, subsequent visits will comprise routine follow-up. If BP is not controlled, the patient may be

> treated consistent with the V side of Protocol I, Visit 3. If the PRA level is below 0.65 and the patient is on both a V and R drug, the patient should be treated consistent with Protocol 1, Visit 6.

Thus, subjects already on one or more V or R or V and R drugs can have their PRA levels measured without having to wait through a washout period. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Second, under the heading "Protocol IIA: For Unresponsive Hypertensive Patients Already Taking V Drug(s)" (at paragraph 116) the specification states at paragraphs 117 and 118:

> In more general terms, as shown in FIG. 5 and Table 7, the Laragh Method provides that a patient still in the titration phase of a single V drug should have the dose of the drug increased to a maximum level as long as the PRA remains below 0.65 ng/ml/hr. In such a patient the sodium volume factor is still operative and contributing to the hypertensive state. Since a renin factor is unlikely to be present in any patient with a low renin level, a patient on any V drug who remains hypertensive with a PRA level less than 0.65 ng/ml/hr is unlikely to respond to any R drug. Therefore, if a full dose of a V drug has already been tested, and assuming good compliance, a V drug with a different mechanism of action should be added. Thus, an exemplary embodiment of the Laragh Method provides that a diuretic can be added to a SARA or vice versa, and then an alpha blocker or CCB, could be added to a diuretic or SARA.
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> Irrespective of whether the hypertensive patient is untreated or treated with a V drug, the higher the PRA level the more likely the patient is to have a renin component to the hypertension. If such an unresponsive patient is already on a full dose of V drug, the Laragh Method provides that an R drug should be added if the patient's PRAlevel is equal to or greater than 0.65 ng/ml/hr. However, if the patient's PRA is equal to or greater than 6.5, the Laragh Method directs that diuretics should be stopped and an R drug started because such high renin levels indicate some dehydration.

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to wait through a washout period. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Third, under the heading "Protocol IIB: For Unresponsive Hypertensive Patients Already Taking R Drug(s)" (at paragraph 119) the specification states at paragraphs 120 and 121:

> Since a renin factor is unlikely to be present in any treated patient with a low renin level (except one treated with a beta blocker), an exemplary embodiment of the Laragh Method provides that any patient on a full dose of a CEI or ARB with a PRA level less than 0.65 ng/ml/hr who remains hypertensive should be switched a V drug.
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> According to an exemplary embodiment of the Laragh Method, a patient with a PRAequal to or greater than 0.65 ng/ml/hr who is unsuccessfully treated with a full dose of any R drug (CEI, ARB or beta blocker) should then have a V drug added as long as PRA is less than 6.5 ng/ml/hr. At or above this level the patient should be treated with a second R drug because, although the three classes of R drugs all block the renin-angiotensin system, they have different sites of action and may be additive for increasing inhibition of the renin system.

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to wait through a washout period. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Fourth, under the heading "Protocol IIC: For Unresponsive Hypertensive Patients Already Taking One or More R and V Drugs" (at paragraph 122) the specification states at paragraphs 123:

> According to an exemplary embodiment of the Laragh Method as indicated in FIG. 5 and Table 7, a PRA test on the first visit is extremely helpful in this situation because it can reveal which mechanism predominates. Thus, PRA values less than 0.65 clearly indicate a sodium-volume excess is present and the patient should be treated as having a primary volume problem. The R drug should be stopped and a second V drug added. Conversely, if the PRA is between 0.65 and 6.5, the anti-renin limb of treatment needs to be strengthened by the addition of a second R drug. Above 6.5 ng/ml/hr, the V drug should be stopped because it may be causing excessive reactive renin secretion. A second R drug can be added, if necessary.

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to wait through a washout period. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Fifth, paragraph 124 states:

> Thus, to summarize, the strategy dictated by an exemplary embodiment of the Laragh Method is to strengthen the V limb for PRA less than 0.65 and stop the anti-renin drugs. When the PRA is between 6.5 and 0.65 an R drug should be added. However, for those patients with PRAs equal to or greater than 6.5, the diuretic therapy should be stopped when the R limb is strengthened because such high renin values are usually associated with sodium volume depletion and overly reactive renin secretion.

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to wait through a washout period. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Sixth, paragraph 129 states:

> Patients with PRA levels above 6.5 ng/ml/hr on V drug(s) may have had a large reactive rise in PRA with the diuretic. If an R drug is added they are likely to have an even greater rise in PRA

> levels which could overwhelm the effects of anti-renin system blockade. In them the V drug should be stopped when the R drug is started. It is possible that such patients may eventually need a second R drug to completely control their BP (dotted arrow).

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to wait through a washout period. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Seventh, paragraph 136 states:

> The Laragh Method as applied to the evaluation and treatment of hypertensive crises is superior to traditional strategies which focus entirely on blood pressure correction per se, perhaps on the assumption that this is the only relevant traditional target. Traditional strategies, however, are faulty because they fail to promptly identify the causal mechanisms, while embodiments of the present invention allow prompt identification of causal mechanisms by immediately exploiting plasma renin testing and the blood pressure responses to specific pharmacologic probes to target causal mechanisms for more specific corrective drug treatments.

Again subjects already on one or more V or R drugs can have their PRA levels measured without having to wait through a washout period. The course of treatment can be determined immediately.

Eighth, paragraph 137 states:

> Thus, in contrast to the Laragh Method, the traditional recommended approaches have relied heavily on I.V. nitroprusside … or oral calcium channel blockers, either of which are seductive because they will in fact at least partially reduce the high blood pressure immediately. But at the same time, whenever there is no mechanistic diagnosis, precious time is lost which could have been used to gain vital diagnostic information about the basic causal mechanisms involving renin-angiotensin and sodium-volume mechanisms.

Thus, subjects who may already be on one or more V or R drugs can have their PRA levels measured without having to wait through a washout period. The course of treatment can be determined immediately.

Accordingly, as evidenced by the eight representative, non-exclusive excerpts from the specification referenced above, the language of the pending claims is fully supported by the specification. More specifically, as shown by these excerpts and elsewhere, the specification teaches that certain embodiments of the invention allow for the immediate use of PRA levels to direct a course of treatment without the need for waiting through what could otherwise be a protracted washout period.

Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Conclusion

In view of the foregoing, applicant respectfully requests that the Examiner allow the presently pending claims, namely claims 26-29.

No fee is believed to be necessary in connection with the filing of this Amendment. If any fees are deemed necessary by the Examiner, applicant hereby authorizes such fee to be charged to Deposit Account No. 50-0540.

If a telephone interview would be of assistance in advancing prosecution of this application, applicant's undersigned attorney encourages the Examiner to telephone him at the number provided below.

Respectfully submitted,

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/Robert E. Alderson/

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